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2,168,939	6 February 1996 (06.02.96)	CA
2,173,820	10 April 1996 (10.04.96)	CA

(71) Applicant *(for all designated States except US)*: PDI-RESEARCH LABORATORIES, INC. [CA/CA]; P.O. Box 353, Station "A", Richmond Hill, Ontario L4C 4Y6 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BEKHAZI, Michel [CA/CA]; 31 Compton Crescent, Pointe Claire, Quebec H9R 5V6 (CA). ZOGHBI, Michel [CA/CA]; Suite 501, 309 Major MacKenzie Drive E., Richmond Hill, Ontario L4C 9V5 (CA).

(74) Agent: HUGHES, ETIGSON; Suite 200, 175 Commerce Valley Drive West, Thornhill, Ontario L3T 7P6 (CA).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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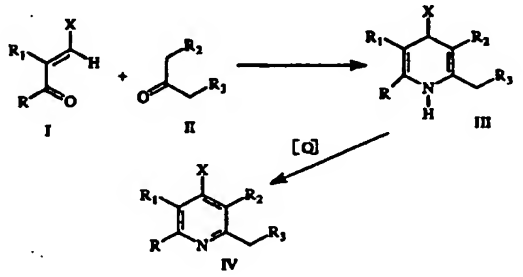
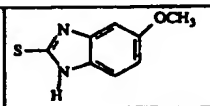
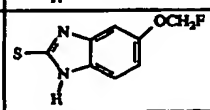
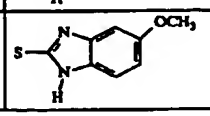
(54) Title: SYNTHESIS OF OMEPRAZOLE-TYPE PYRIDINE DERIVATIVES AND INTERMEDIATES THEREOF

(57) Abstract

A process of reacting (a) is provided wherein R, R_1, R_2, R_3 and X are selected from (b).



(b)

R	R_1	R_2	R_3	X	To produce the Medicine identified below:
H	CH_3	CH_3		OCH_3	Omeprazole
H	H	OCH_3		OCH_3	Pantoprazole
H	H	CH_3		OCH_2CF_3	Lansoprazole

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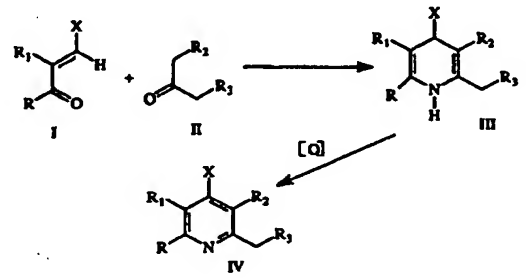
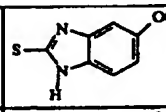
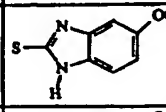
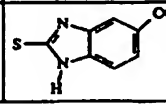


(b)

R	R_1	R_2	R_3	X	To produce the Medicine identified below:
H	CH_3	CH_3		OCH_3	Omeprazole
H	H	OCH_3		OCH_3	Pantoprazole
H	H	CH_3		OCH_2CF_3	Lansoprazole

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TITLE OF INVENTION

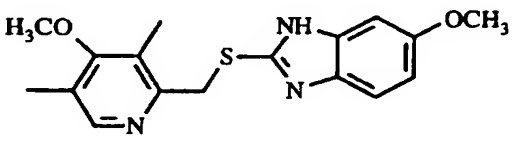
SYNTHESIS OF OMEPRAZOLE-TYPE PYRIDINE DERIVATIVES AND INTERMEDIATES THEREOF

FIELD OF INVENTION

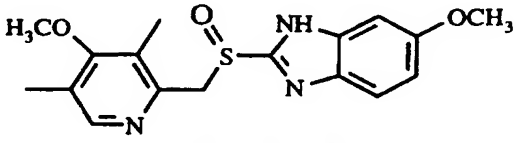
This invention relates to the manufacture of Omeprazole, intermediates suitable for the manufacture of Omeprazole and the use thereof to manufacture Omeprazole. This invention in its broadest aspects is directed to the manufacture of medicines such as Omeprazole, Pantoprazole, and Lansoprazole, intermediates suitable for the use to manufacture each of the medicines and the processes using those intermediates to manufacture the medicines.

BACKGROUND OF INVENTION

Omeprazole was discovered by Hassel chemists, and is derived from the oxidation of intermediate 1'.

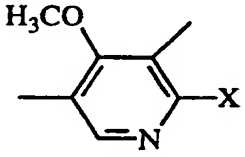


Intermediate 1'

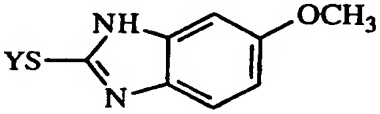


Omeprazole

Intermediates 2' and 3' are coupled to give 1.



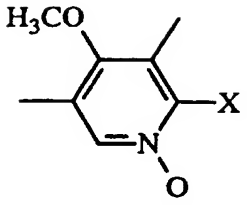
Intermediate 2'



Intermediate 3'

(See for example Canadian Letters Patent No. 1,127,158)

Because the intermediates leading to the pyridine entity were very unstable, Hassel came up with the following starting intermediate, where the oxygen on the nitrogen is eliminated at the stage when X is converted from methyl to hydroxymethyl.



Intermediate 4

(See Canadian Letters Patent No. 1,234,118)

EP 484,265 (Esteve) on the other hand, carried the synthesis with either of chloro or nitro at the 4 position. Once the skeleton was built, Esteve either substituted at the 4 position with methoxy and then reduced the nitroso or vice-versa.

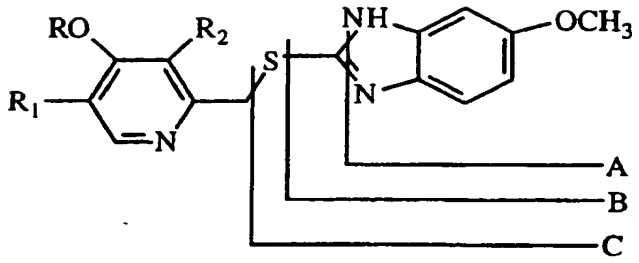
US 5,374,730 (Torcan) purports to teach the manufacture of Omeprazole free from highly coloured impurities. Torcan achieves that result by making a solid intermediate, that can be crystallized. To this end, Torcan oxidized their substituted thioether and obtained a water soluble crystalline intermediate which upon decarboxylation yielded pure water insoluble Omeprazole.

Applicant is also aware of new and efficient oxidizing agents used for converting the thioether to S=O purportedly taught by recent Takeda (CA 1,263,119) and Hassel's (U.S. 5,386,032) patents.

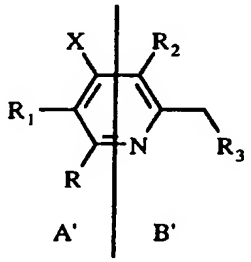
Applicant has now discovered a novel method for the manufacture of Omeprazole, Pantoprazole and Lansoprazole and related medicines which Applicant believes is efficient and suitable to produce these medicines.

These methods are to be used to build substituted pyridines (useful pharmaceutical intermediates), which could be used as precursors for the synthesis of Omeprazole, Pantoprazole or Lansoprazole and related medicines.

In all the published synthesis covering Omeprazole or Lansoprazole, the appropriately substituted pyridine was reacted with A, B or C synthons.

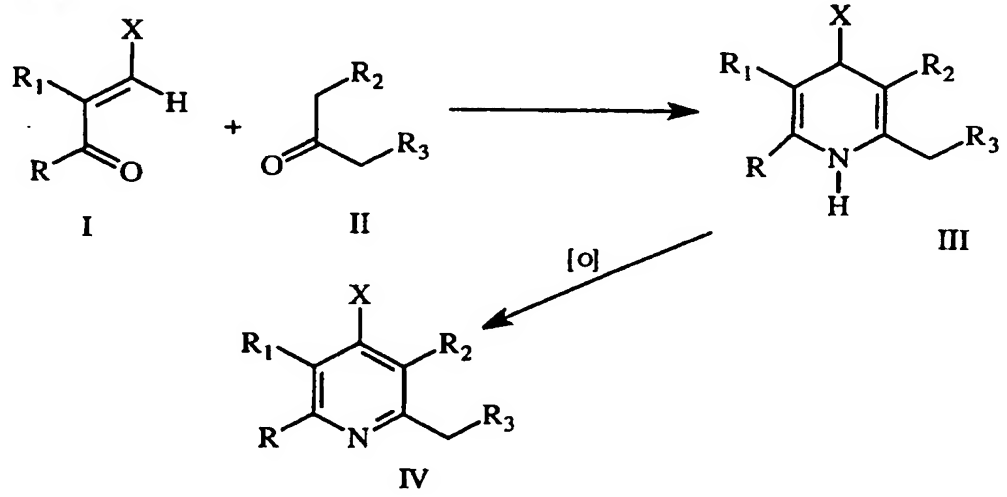


Applicant believes that the following approach would be highly suitable for use to make pyridines which are intermediates that could be used to make medicines. Applicant proposes that the following pyridine compound:



could be prepared by the following scheme of reaction (in suitable solvents):

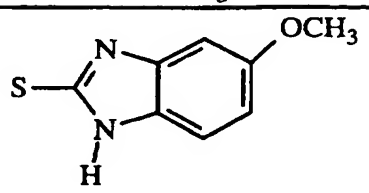
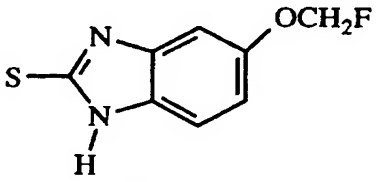
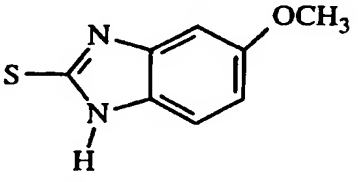
Scheme 1:



(Intermediate II is available. Intermediate I is generally known and may be prepared using methods known in the literature such as:

1. Lou, J.-D.; Lou, W.-X. *Synthesis*, **1987**, 179 (and references cited therein).
2. E. Breitmaier; S. Gassenmann, *Chem. Ber.*, **1971**, 104, 665.
3. Kalina, N.N.; Klimko, V.T.; Protopopova, T.-V; Skoldinor, A.P. *Zh. Obshch. Khim.* **1962**, 32, 2146, C.A., 58, 7825 g.
4. Klimko, V.T.; Protopopova, T.-V.; Smirnova, N.V.; Skoldinov, A.P. *Zh. Obshch. Khim.* **1962**, 32, 2961.
5. Kalinina, N.N.; Klimko, V.T.; Protopopova; Skoldinov, A.P. *J. Gen. Chem. USSR (Engl. Transl.)*, **1962**, 32, 2116.
6. Klimko, V.T.; Protopopova, N.V.; Smirnova, N.V.; Skoldinov, A.P. *J. Gen. Chem. USSR (Engl. Transl.)*, **1962**, 32, 2913.
7. Wang, Chia-Lin J.; Salvino, J.M., *Tetrahedron Lett.* **1984**, 25(46), 5243-6.
8. Seebach D., *Chem. Ber.* **1972**, 102, 487.
9. Solladié, G.; Ruiz, P.; Colobert, F.; Carreno, M.C.; Garcia Ruano, J.L. *Synthesis* **1991**, 1011.
10. Thummel, R.P.; Kohli, D.K. *J. Org. Chem.* **1977**, 42, 2742.
11. Moller, R.; Engel, N.; Steglich, W. *Synthesis*, **1978**, 621.
12. Ullrich, F.-W.; Breitmaier *Synthesis*, **1983**, 641.
13. Menicagli, R.; Malanga, C.; Guidi, M.; Lardicci, L. *Tetrahedron*, **1987**, 43(1), 171 (and references cited therein).
14. Breitmaier, E.; Ullrich, F.W.; Potthoff, B.; Bohme, R.; Bastian, H. *Synthesis*, **1987**, 1 (Ubersicht).
15. Hertenstein, U.; Hunig, S.; Oller, M. *Chem. Ber* **1980**, 113, 3783.
16. Ruegg, R.; Lindlar, H.; Montavon, M.; Saucy, G.; Schaeren, S.F.; Schwieter, U.; Isler, O. *Helv. Chim. Acta* **1959**, 42, 847.
17. Nair, V.; Vietti, D.E.; Cooper, C.S. *J. Am. Chem. Soc.*, **1981**, 103, 3030.
18. Gagan, J.M.F.; Lloyd, D. *Chem. Comm.* **1967**, 1043.
19. Weibenfels, M.; Schurig, H.; Huhsam, G. *Chem. Ber.*, **1967**, 100, 584.
20. Todoriki, R.; Ono, M.; Tamura, S. *Heterocycles*, **1986**, 24(3), 775.
21. Eskenazi, P.C.; Maitte, P. *Bull. Soc. Chim.* **1976**, 995.
22. Farina, F.; Gomez, M.J.; Martin, M.V. *An. Quim.* **1974**, 70(12), 900-4.
23. Farina, F.; Victory, P. *Tetrahedron Lett.* **1969**, 38, 3219-22.

Intermediates I and II are selected to form A' and B' (the halves of the pyridine molecule). III is converted to the final product IV by oxidation [O]. The substituents R, R_1, R_2, R_3 and X are chosen having regard to the substituents on the medicines. Thus, the following combinations present themselves:

R	R_1	R_2	R_3	X	Medicine
H	CH_3	CH_3		OCH_3	Omeprazole
H	H	OCH_3		OCH_3	Pantoprazole
H	H	CH_3		OCH_2CF_3	Lansoprazole

or R may be selected from:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_1 may be selected from:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_2 may be selected from:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_3 may be selected from:

Alkoxy
Hydroxy
Halogen

Activated Ester
Tosylate
Mesylate
Thiol
Xanthyl

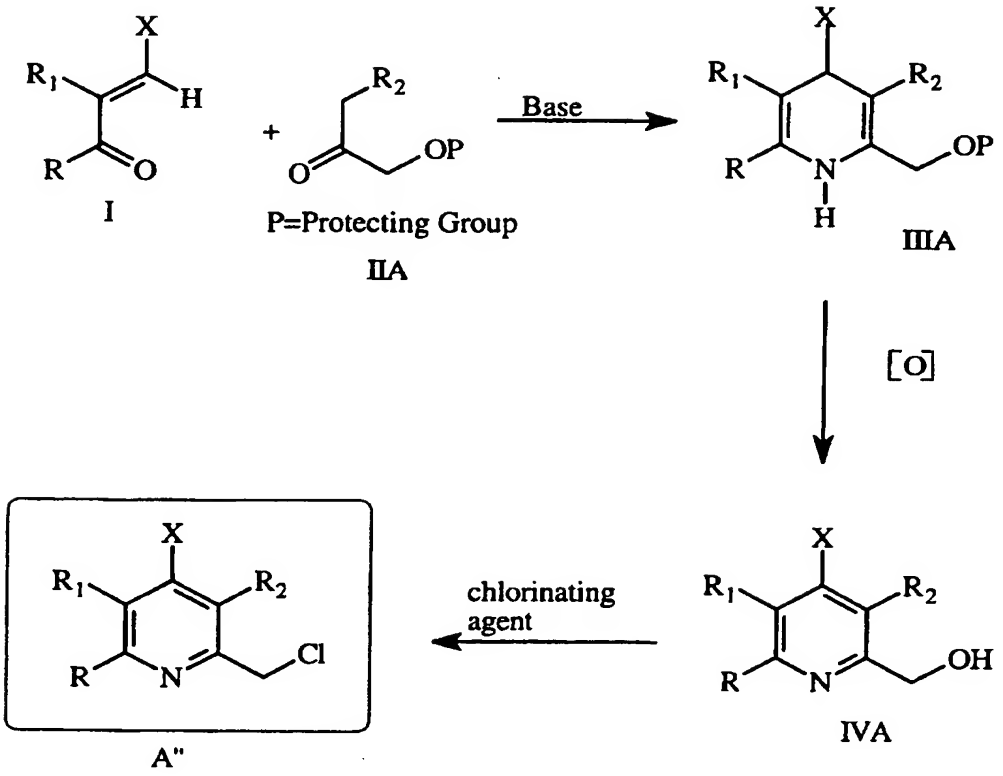
and X may be selected from:

Alkoxy
Halogen
Nitro
Cyano
Carboxyl
Alkyl
H

Compound III is novel and the precursor for the medicines identified above (Omeprazole, Pantoprazole and Lansoprazole).

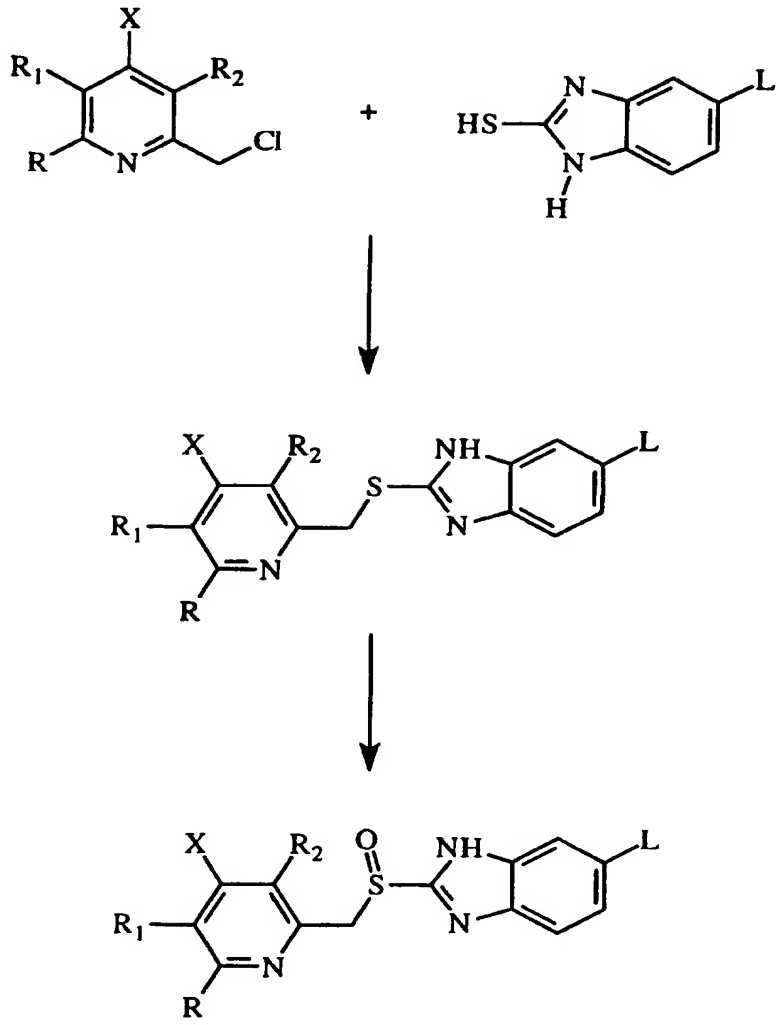
Compound III may also be an intermediate where R_3 is a leaving group such as Halogen (for example chlorine, bromine, fluorine and the like) or a protected oxygen (OP where P is a protecting group). In this regard, intermediate "A"", useful to make the above medicines, may be made from intermediate IIIA where R_3 is OP (where P= a protecting group).

The following synthesis based on building intermediate "A"" set out below presents itself:



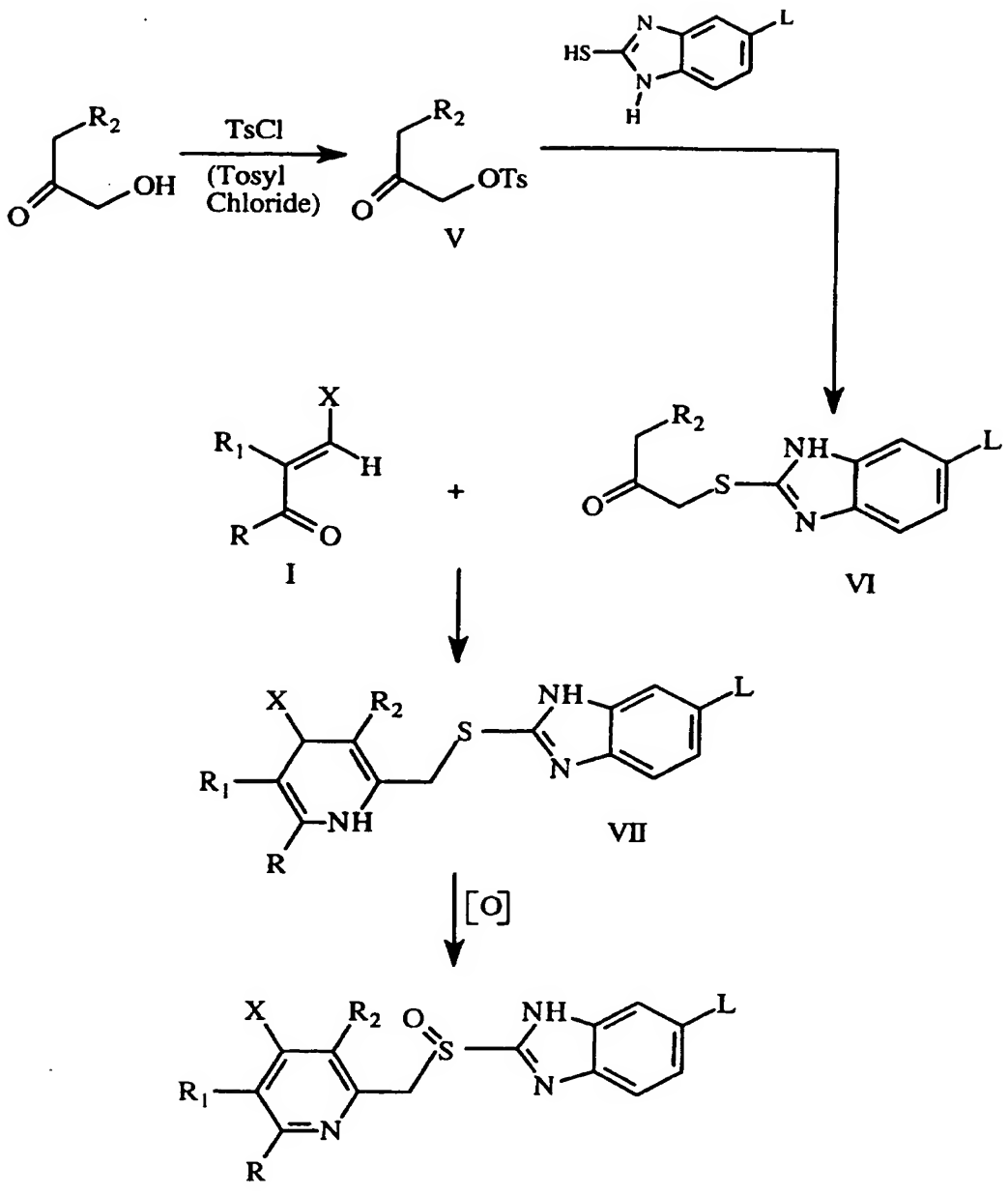
Compound IIA may be prepared from the corresponding alcohol and a suitable protecting group (e.g. tetrahydropuranyl, tert-butyldimethyl silyl, etc.). Other protecting groups like esters, carbonates and substituted methyl, ethyl, benzyl or silyl esters can also be used.

Intermediate A" is then used to manufacture one of the three medicines, as follows:



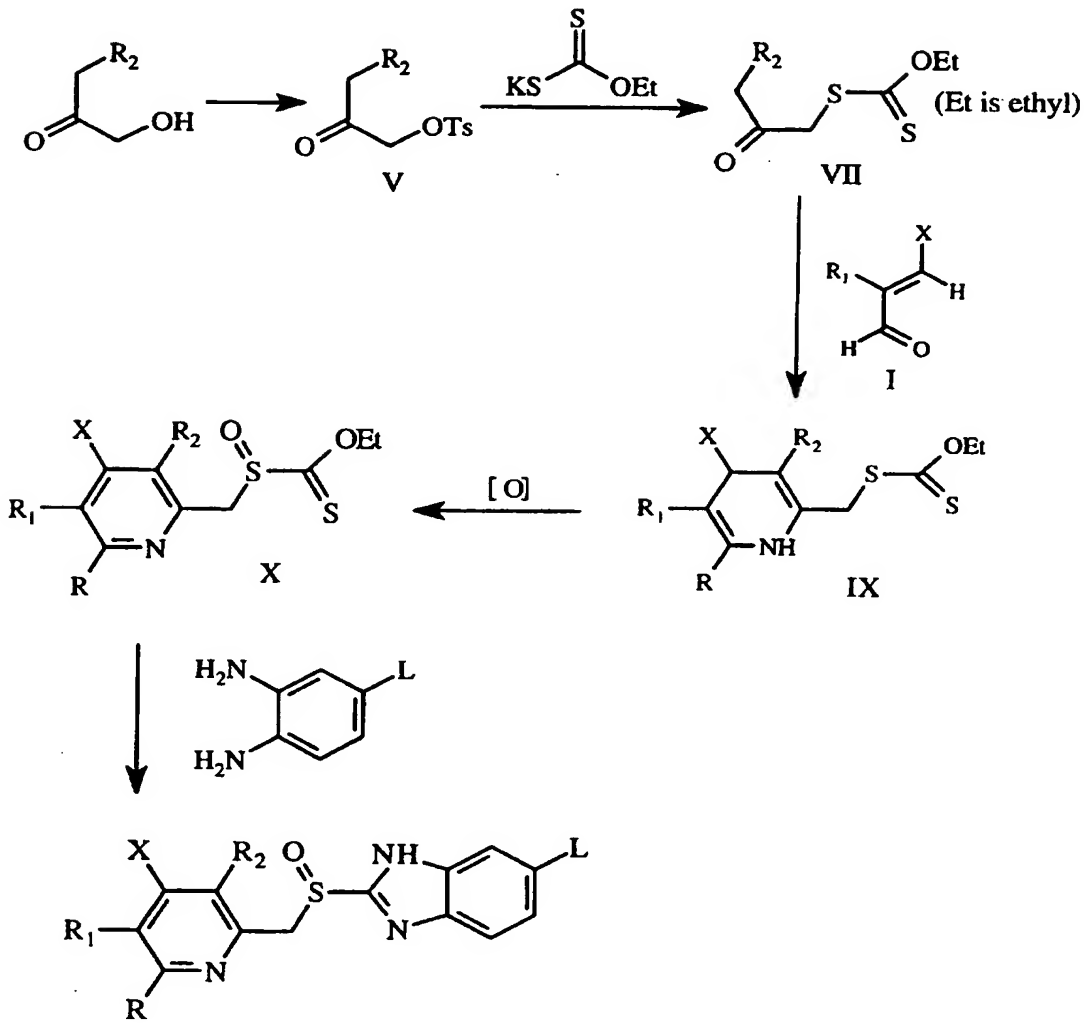
wherein R, R_1, R_2 and X are defined above in the chart and L is selected from OCH_3 and OCH_2F.

Additionally, the pyridine may be built last so that all constituents of the molecules are attached to a skeleton first, and then the pyridine is completed last. For example, the following scheme presents itself. (Synthesis based on building the pyridine last):



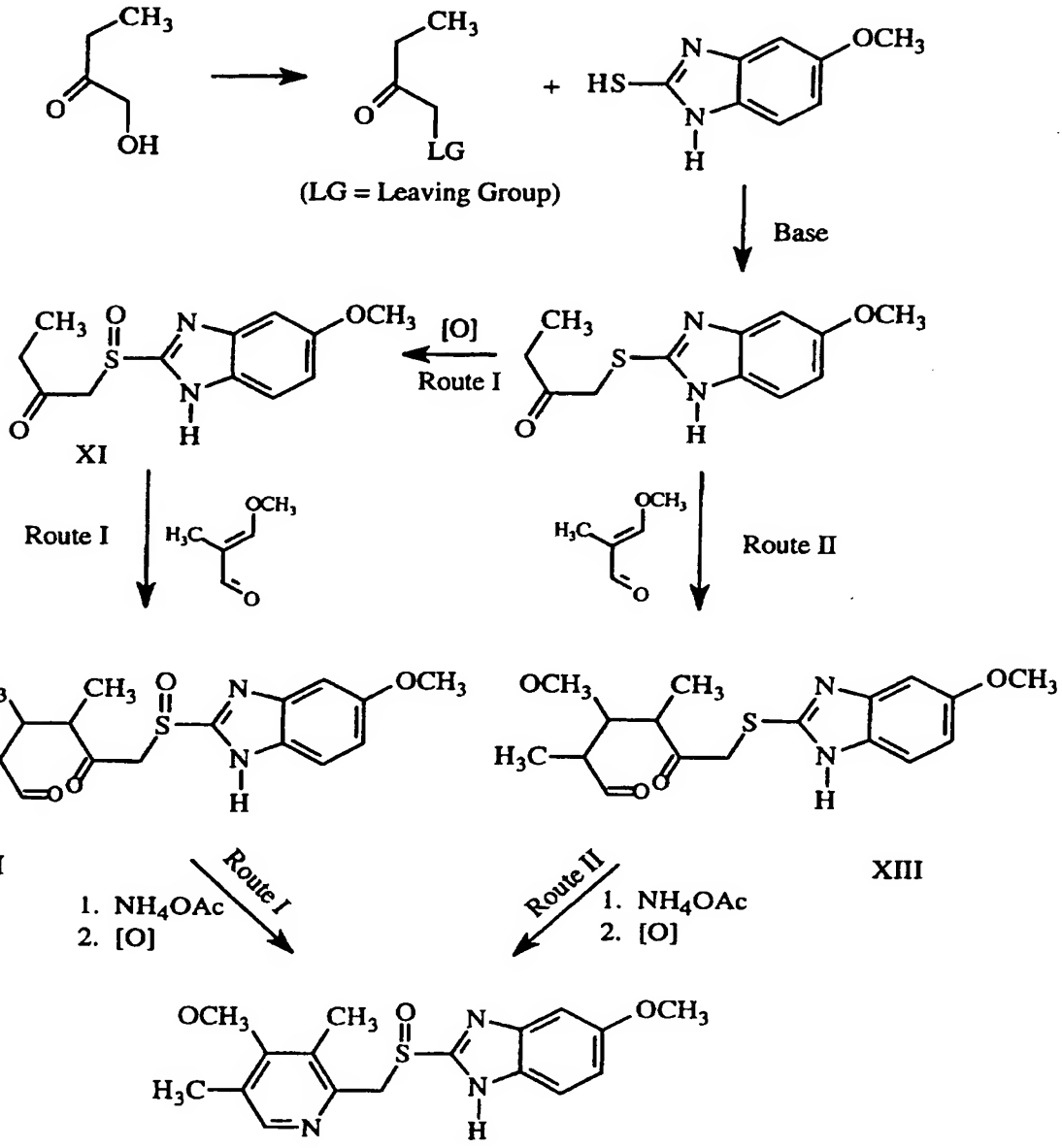
wherein R, R_1, R_2, X and L are defined as previously.

In another scheme, the Benzimidazole is built last:



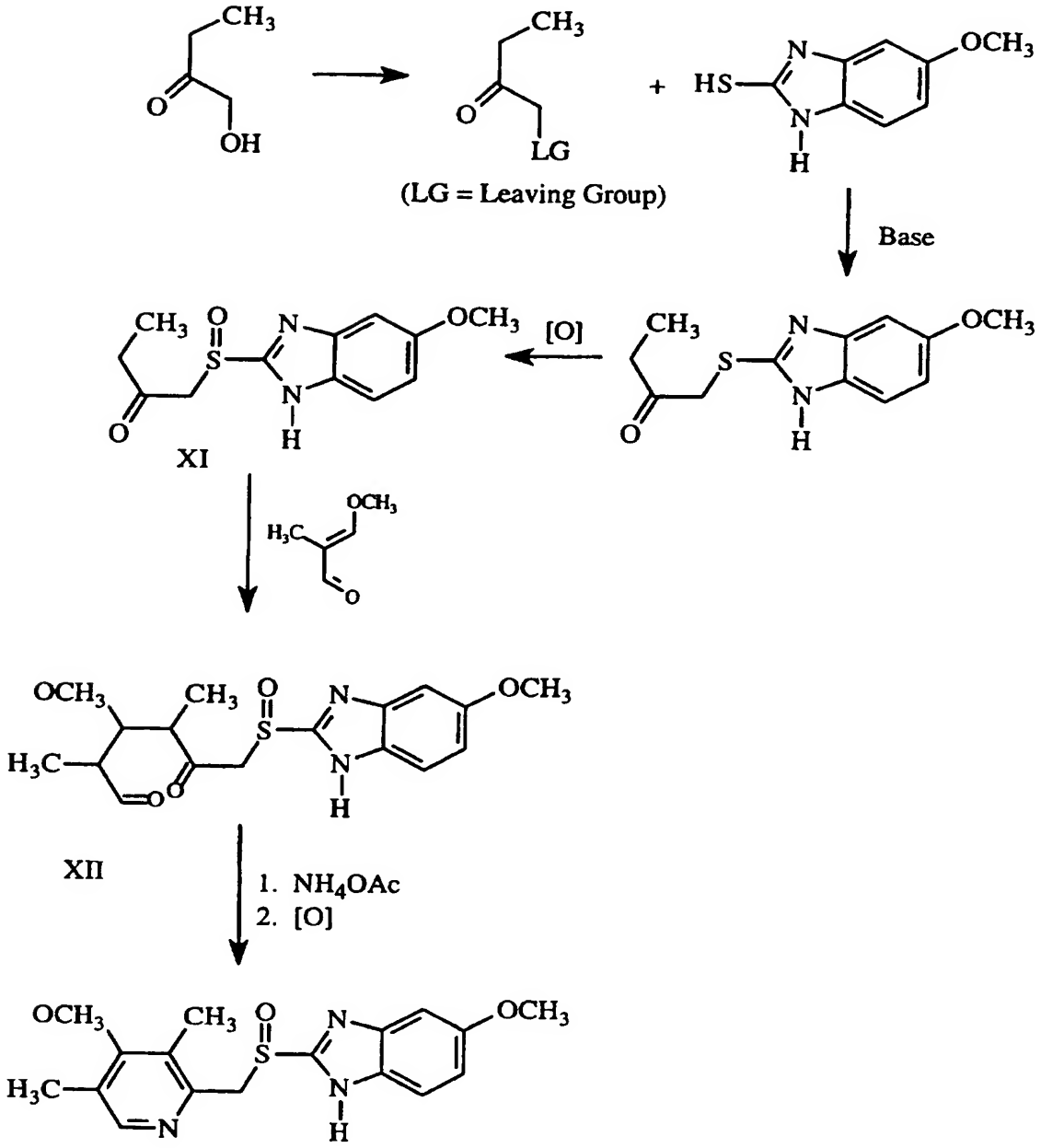
wherein R, R_1, R_2, X and L are as previously described.

According to other aspects of the invention, the processes may be carried out as follows:

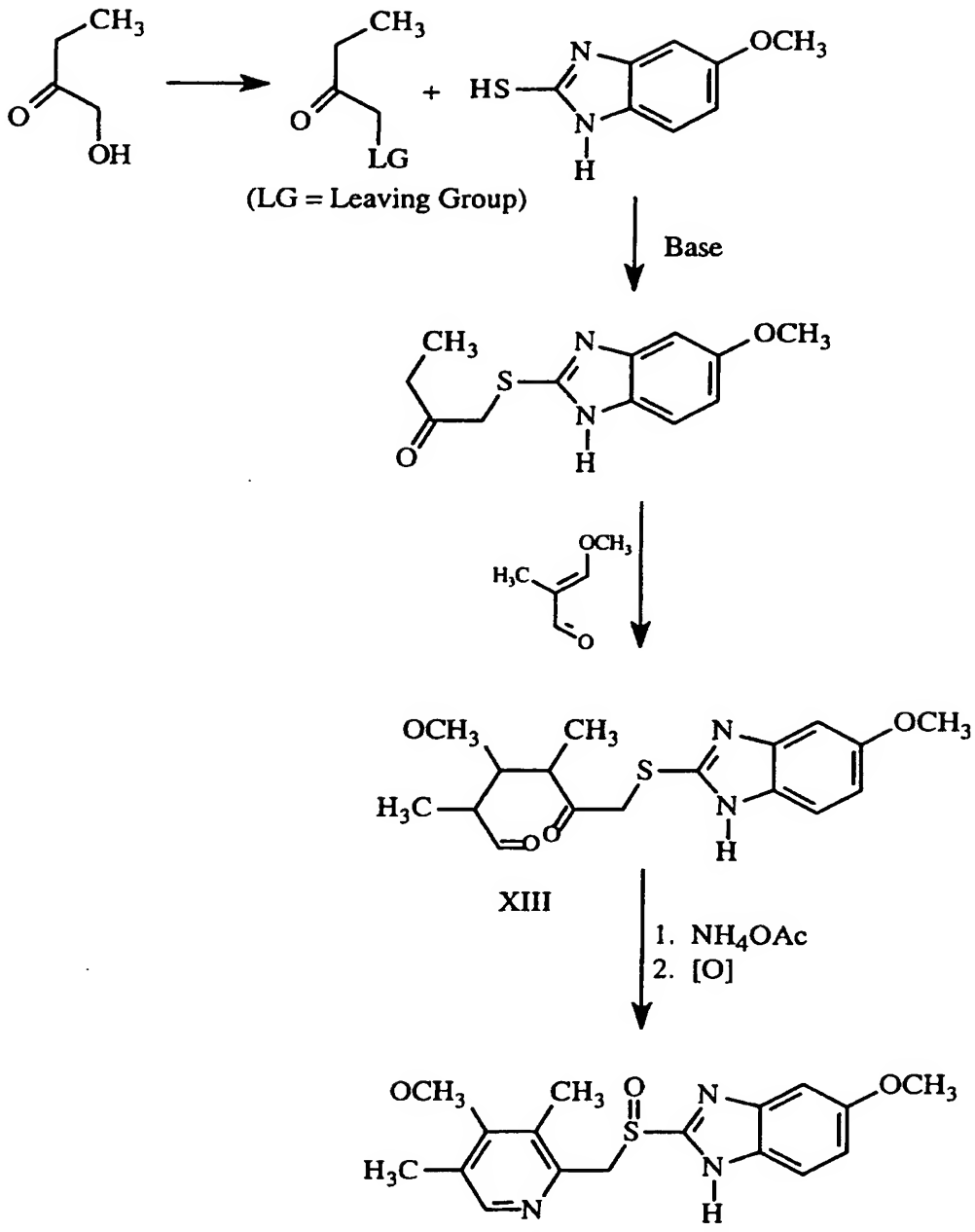


Thus the following processes in schematic form are established:

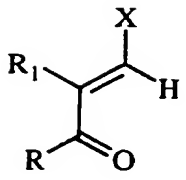
ROUTE I


CH3
O
OH
CH3
O
LG
(LG = Leaving Group)
+
HS
N
N
H
OCH3
Base
CH3
O
S
N
N
H
OCH3
O
[O]
CH3
O
S
N
N
H
OCH3
O
XI
OCH3
H3C
O
OCH3
CH3
O
S
N
N
H
OCH3
H3C
O
O
XII
1. NH4OAc
2. [O]
OCH3
CH3
O
S
N
N
H
OCH3
H3C
N

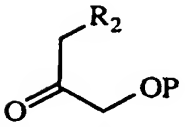
ROUTE II



Compounds I, IIA, III, IIIA, VI, VII, VIII, IX, X, XI, XII and XIII following, are new:

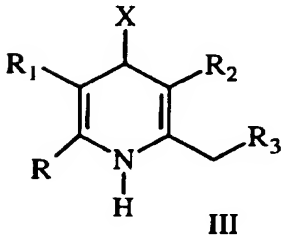


I

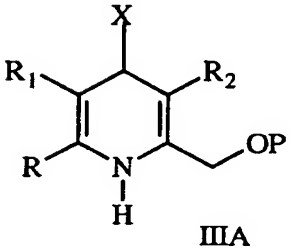


P=Protecting Group

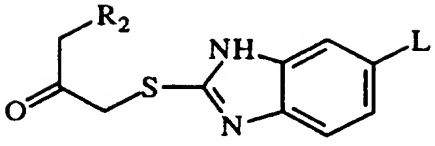
IIA



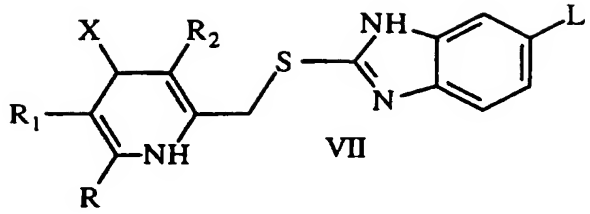
III



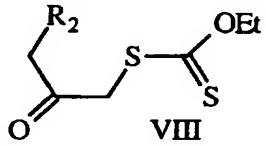
IIIA



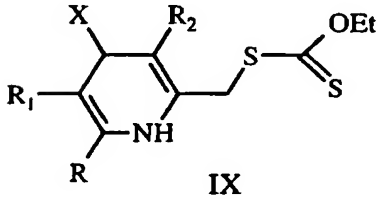
VI



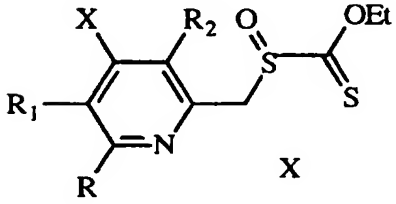
VII



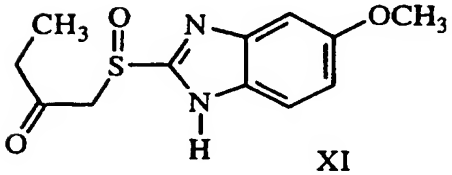
VIII



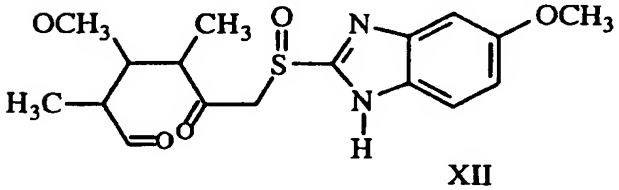
IX



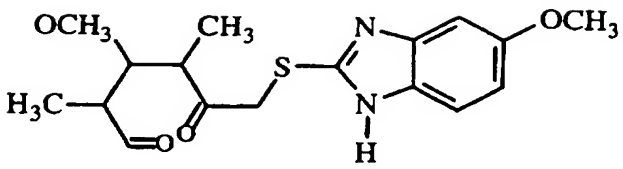
X



XI



XII



XIII

R, R1, R2, R3, and X are as defined above.

The invention will now be illustrated with reference to the following proposed examples.

Example 1:

Synthesis of the chloro pyridine (scheme relating to building intermediate "A")

A base (e.g. Potassium t-Butoxide) (1.0 eq) will be added to a cooled solution (-20 to O C) of the protected hydroxy ketone (1.0 eq) in dry tetrahydrofuran (THF). A THF solution of the α,β unsaturated carbonyl (1.0 eq), would then be added dropwise. At the end of the reaction, ammonium chloride/ammonia (3.0 eq) will be added and the reaction mixture stirred at room temperature. Water may then be added to the mixture and the organic product extracted in toluene. The crude dihydropyridine will then be extracted with an acidic aqueous solution (sulfuric acid).

To the aqueous solution, nitric acid will be added and the mixture heated to reflux until the oxidation is complete. The solution will then be slowly cooled to O C. Crushed ice will then be added followed by ammonium hydroxide until the mixture is alkaline. The solid is then isolated and washed with cold water. The crude product will be recrystallized from alcohol.

Other oxidizing agents could be used to oxidize the dihydropyridine to the pyridine, e.g. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

The 2-Chloromethyl pyridine "Intermediate A" can be prepared by reacting the 2-hydroxymethylpyridine with thionylchloride (according to *Arch. Pharm.* Vol. 26 pp. 448-451 (1956)).

Example 2:

Based on the scheme for building the pyridine last.

Tosylchloride (1.0 eq) is added to a solution of the hydroxy ketone (1.0 eq) and base (e.g. triethylamine) (1.0 eq) in a suitable solvent (e.g. toluene, methylene chloride). The mercaptobenzimidazole sodium salt (1.0 eq) will be added to the tosylate solution. At the end of the

reaction, the mixture will be washed successively with water, a saturated solution of sodium bicarbonate and brine. The organic extract will be dried over sodium sulfate, filtered and will be rotary evaporated to yield the crude product.

Example 3:

Benzimidazole formation (synthesis based on building the imidazole last)

Xanthate (1.0 eq) and the tosylate (1.0 eq) will be reacted in a solvent (e.g. ethanol) at reflux. When the reaction is complete, the solvent will be replaced with toluene and the organic layer will be washed with water and brine. The toluene is then rotary evaporated, THF will be added, and the solution cooled (-20 to O C).

A base (e.g. Potassium t-Butoxide) (1.0 eq) is added to the cooled solution of the xanthate adduct. A THF solution of the α,β unsaturated carbonyl (1.0 eq), is then added dropwise. At the end of the reaction, ammonium chloride/ammonia (3.0 eq) will be added and the reaction mixture stirred at room temperature. Water will be added to the mixture and the organic product extracted in toluene. Toluene will be rotary evaporated and the crude product will be used for the next step.

m-Chloroperbenzoic acid (2.0 eq) will be dissolved in chloroform, cooled to O C and added to the cooled chloroform solution (O C) of the dihydropyridine. The mixture will be stirred overnight at room temperature, filtered, and washed with 10% $NaHCO_3$, and dried over sodium sulfate. Filteration and rotary evaporation afford the crude product.

The crude product and 5-substituted phenylenediamine (1.0 eq) will be dissolved in toluene that contained TFA (1.0 eq). The mixture will be refluxed until the reaction is complete. At the end of the reaction, the mixture will be cooled, 10% NaOH will then be slowly added until the mixture is just alkaline. The crude benzimidazole will be then filtered, washed with water and recrystallized from alcohol.

Example 4:

Intermediate I which is 3-methoxy, 2-methyl, 2-propenal, may be prepared as follows:

Methanesulfonyl chloride (1 eq.) will be added to a solution of methylmalondialdehyde sodium salt (prepared by a literature procedure involving the Vilsmeier-Haack-Arnold acylation of propionaldehyde diethyl acetal: Nair, V.; Vietti, D.E.; Cooper, C.S. *J. Am. Chem. Soc.* **1981**, 103, 3030-3036) (1 eq.) in a suitable solvent

(e.g. methylene chloride, toluene). The mixture will be stirred at room temperature until the reaction is complete. At the end of the reaction, the product will be concentrated on the rotary evaporator and dissolved in anhydrous methanol. The mesylate methanol solution will then be added to a sodium methoxide (1-5 eq.) solution in the same solvent. The mixture will be stirred at room temperature until the reaction is complete. The product will be concentrated on the rotary evaporator, dissolved in methylene chloride (or other suitable solvent, e.g. toluene) and washed consecutively with saturated aqueous ammonium chloride, water, and brine. The solution will then be dried over anhydrous sodium sulfate, filtered, and rotary evaporated to yield the crude 3-methoxy, 2-methyl, 2-propenal (I).

Other specific intermediate (I) compounds can be prepared by persons skilled in the art having regard to the articles referred to herein and the above teachings.

Example 5:

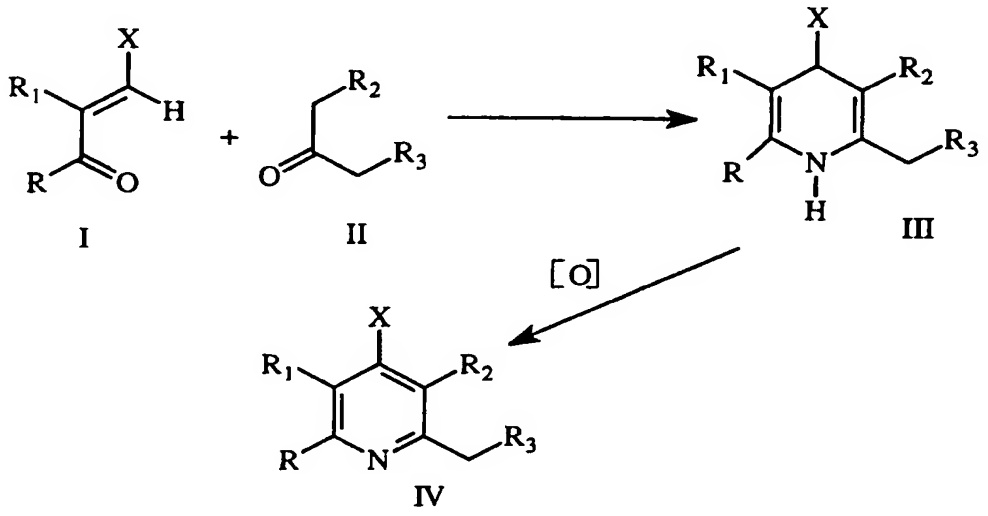
The product from example 2 will be oxidized (route I, found at page 12 of the application) by reaction with MCPBA in methylene chloride. The product will be isolated after pH adjustment by extraction and evaporation.

The Michael, aminolysis, cyclization and oxidation of the resulting dihydropyridine will be then achieved as in example 1.

As many changes can be made to the invention without departing from the scope of the invention, it is intended that all material herein be interpreted as illustrative of the invention and not in a limiting sense.

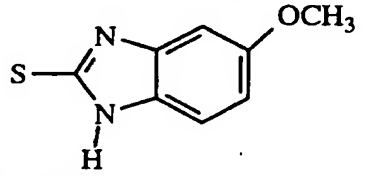
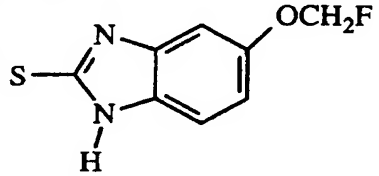
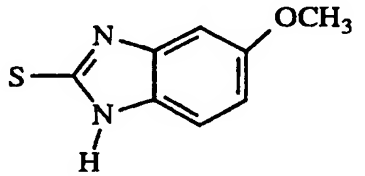
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A process of reacting:



I II III IV

is provided wherein R, R_1, R_2, R_3 and X are selected from:

R	R_1	R_2	R_3	X	To produce the Medicine identified below:
H	CH_3	CH_3		OCH_3	Omeprazole
H	H	OCH_3		OCH_3	Pantoprazole
H	H	CH_3		OCH_2CF_3	Lansoprazole

or R may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_1 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_2 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

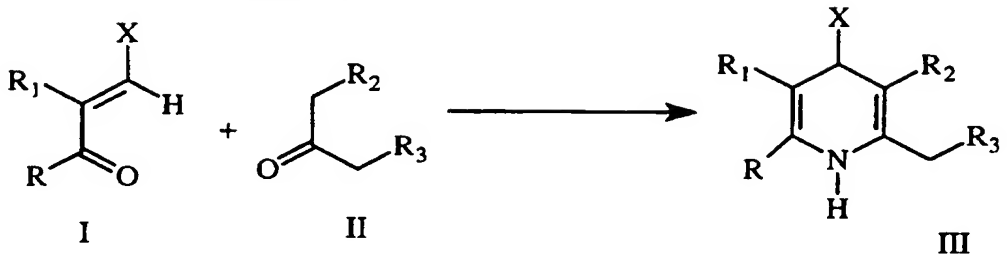
R_3 may be selected from the group consisting of:

Alkoxy
Hydroxy
Halogen
Activated Ester
Tosylate
Mesylate
Thiol
Xanthyl

and X may be selected from the group consisting of:

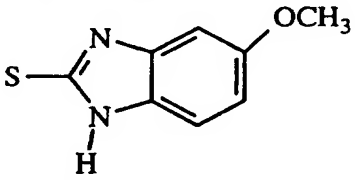
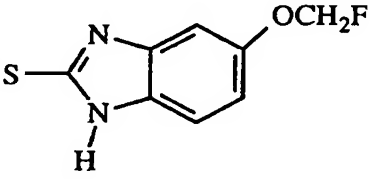
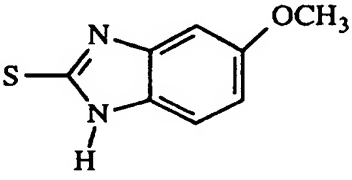
Alkoxy
Halogen
Nitro
Cyano
Carboxyl
Alkyl
H

2. The process of:



I II III

wherein R, R_1, R_2, R_3 and X are selected from the following group:

R	R_1	R_2	R_3	X	To produce the Medicine identified below:
H	CH_3	CH_3		OCH_3	Omeprazole
H	H	OCH_3		OCH_3	Pantoprazole
H	H	CH_3		OCH_2CF_3	Lansoprazole

or R may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_1 may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

R_2 may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

R_3 may be selected from the group consisting of:

Alkoxy

Hydroxy

Halogen

Activated Ester

Tosylate

Mesylate

Thiol

Xanthyl

and X may be selected from the group consisting of:

Alkoxy

Halogen

Nitro

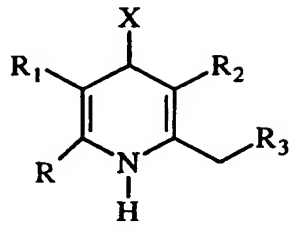
Cyano

Carboxyl

Alkyl

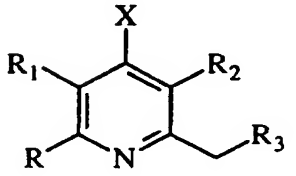
H

3. The process of reacting:



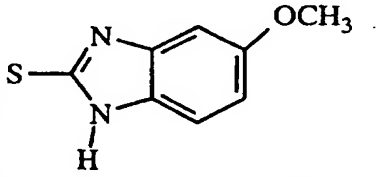
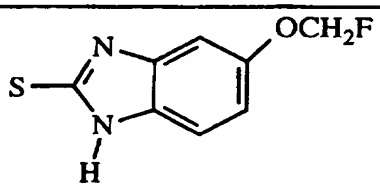
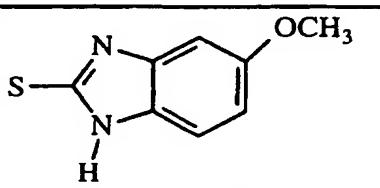
III

to produce:



IV

wherein the substituents R, R_1, R_2, R_3 and X are selected as follows:

R	R_1	R_2	R_3	X	To produce the Medicine identified below:
H	CH_3	CH_3		OCH_3	Omeprazole
H	H	OCH_3		OCH_3	Pantoprazole
H	H	CH_3		OCH_2CF_3	Lansoprazole

or R may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_1 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_2 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_3 may be selected from the group consisting of:

Alkoxy
Hydroxy
Halogen
Activated Ester
Tosylate
Mesylate
Thiol
Xanthyl

and X may be selected from the group consisting of:

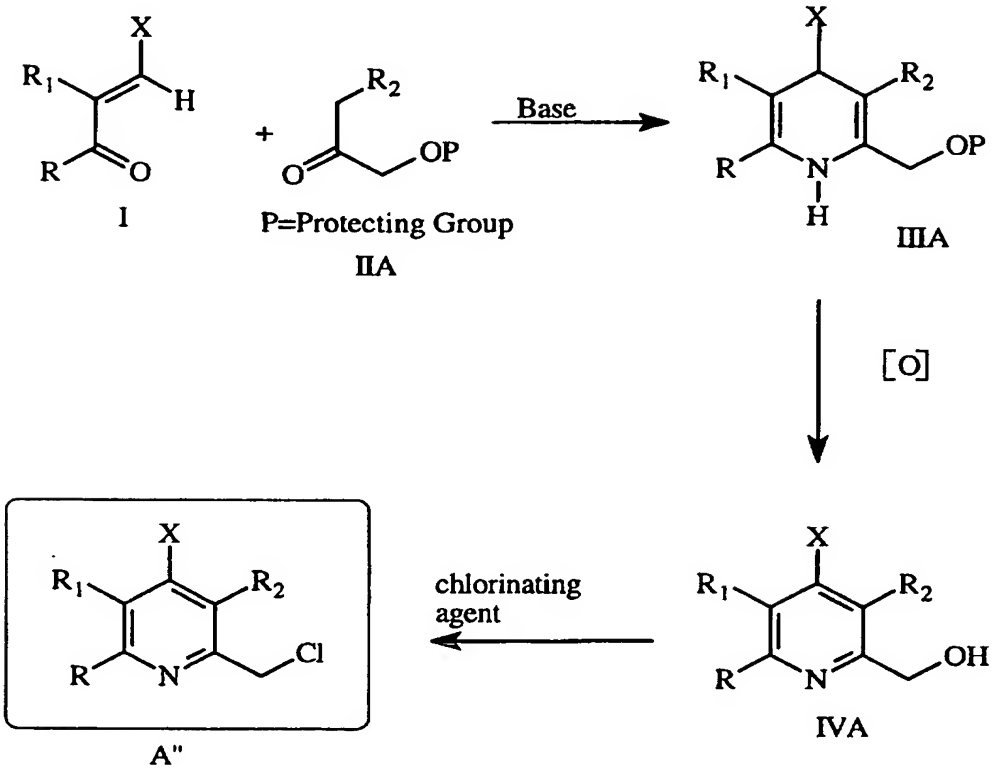
Alkoxy
Halogen
Nitro
Cyano
Carboxyl
Alkyl
H

4. The process of claim 1 or 3 wherein the medicine Omeprazole is produced.

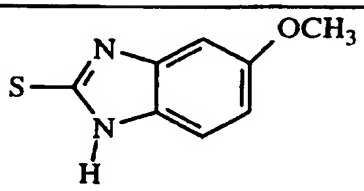
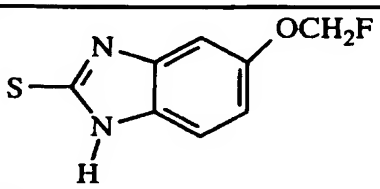
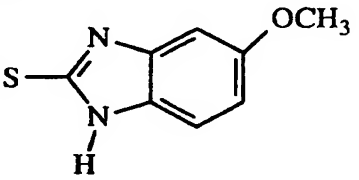
5. The process of claim 1 or 3 wherein the medicine Pantoprazole is produced.

6. The process of claim 1 or 3 wherein the medicine Lansoprazole is produced.

7. The process of reacting:



wherein R, R_1, R_2, R_3 and X are selected from:

R	R_1	R_2	R_3	X	To produce the Medicine identified below:
H	CH_3	CH_3		OCH_3	Omeprazole
H	H	OCH_3		OCH_3	Pantoprazole
H	H	CH_3		OCH_2CF_3	Lansoprazole

or R may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

R_1 may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

R_2 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

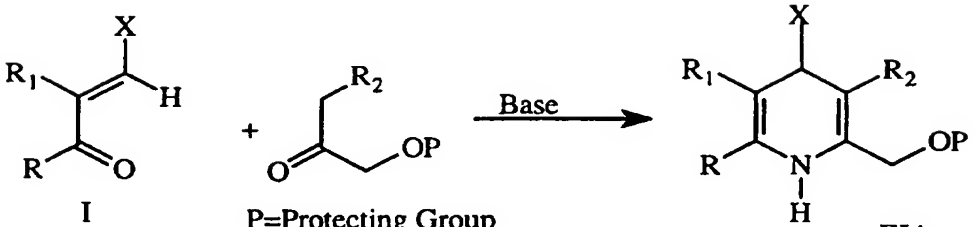
R_3 may be selected from the group consisting of:

Alkoxy
Hydroxy
Halogen
Activated Ester
Tosylate
Mesylate
Thiol
Xanthyl

and X may be selected from the group consisting of:

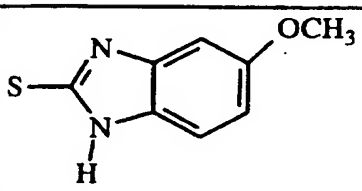
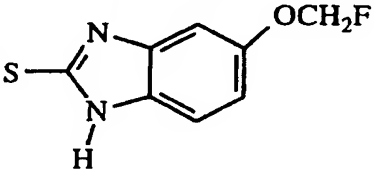
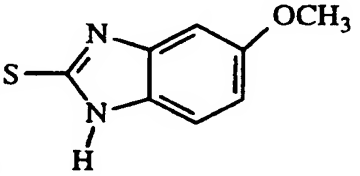
Alkoxy
Halogen
Nitro
Cyano
Carboxyl
Alkyl
H

8. The process of reacting:



I P=Protecting Group IIA IIIA

wherein R, R_1, R_2, R_3 and X are selected from:

R	R_1	R_2	R_3	X	To produce the Medicine identified below:
H	CH_3	CH_3		OCH_3	Omeprazole
H	H	OCH_3		OCH_3	Pantoprazole
H	H	CH_3		OCH_2CF_3	Lansoprazole

or R may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

R_1 may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

R_2 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

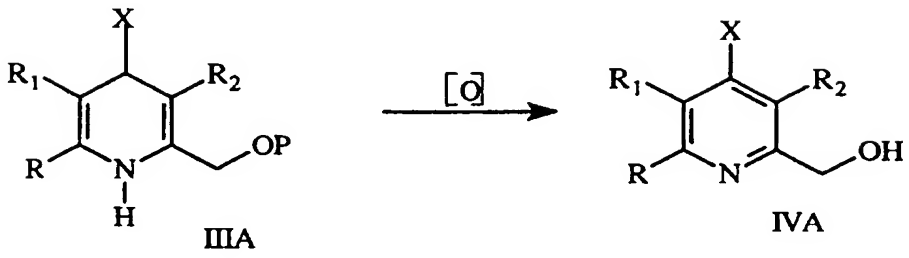
R_3 may be selected from the group consisting of:

Alkoxy
Hydroxy
Halogen
Activated Ester
Tosylate
Mesylate
Thiol
Xanthyl

and X may be selected from the group consisting of:

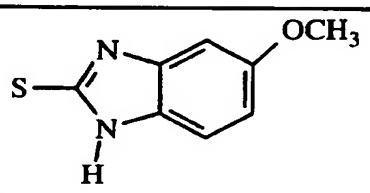
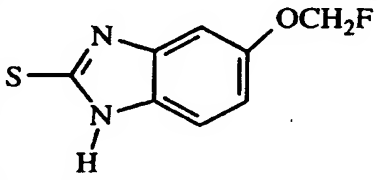
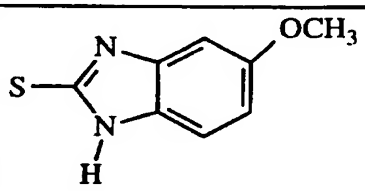
Alkoxy
Halogen
Nitro
Cyano
Carboxyl
Alkyl
H

9. The process of reacting:



IIIA IVA

wherein R, R_1, R_2, R_3 and X are selected from:

R	R_1	R_2	R_3	X	To produce the Medicine identified below:
H	CH_3	CH_3		OCH_3	Omeprazole
H	H	OCH_3		OCH_3	Pantoprazole
H	H	CH_3		OCH_2CF_3	Lansoprazole

or R may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

R_1 may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

R_2 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

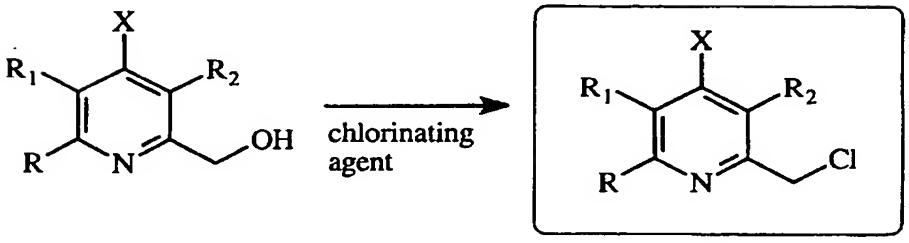
R_3 may be selected from the group consisting of:

Alkoxy
Hydroxy
Halogen
Activated Ester
Tosylate
Mesylate
Thiol
Xanthyl

and X may be selected from the group consisting of:

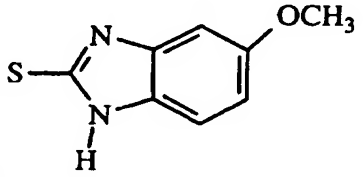
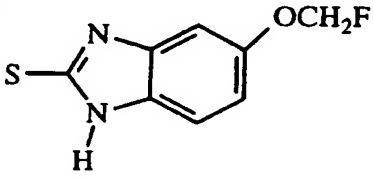
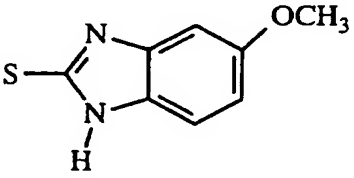
Alkoxy
Halogen
Nitro
Cyano
Carboxyl
Alkyl
H

10. The process of reacting:



A"

wherein R, R_1, R_2, R_3 and X are selected from:

R	R_1	R_2	R_3	X	To produce the Medicine identified below:
H	CH_3	CH_3		OCH_3	Omeprazole
H	H	OCH_3		OCH_3	Pantoprazole
H	H	CH_3		OCH_2CF_3	Lansoprazole

or R may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

R_1 may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

R_2 may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

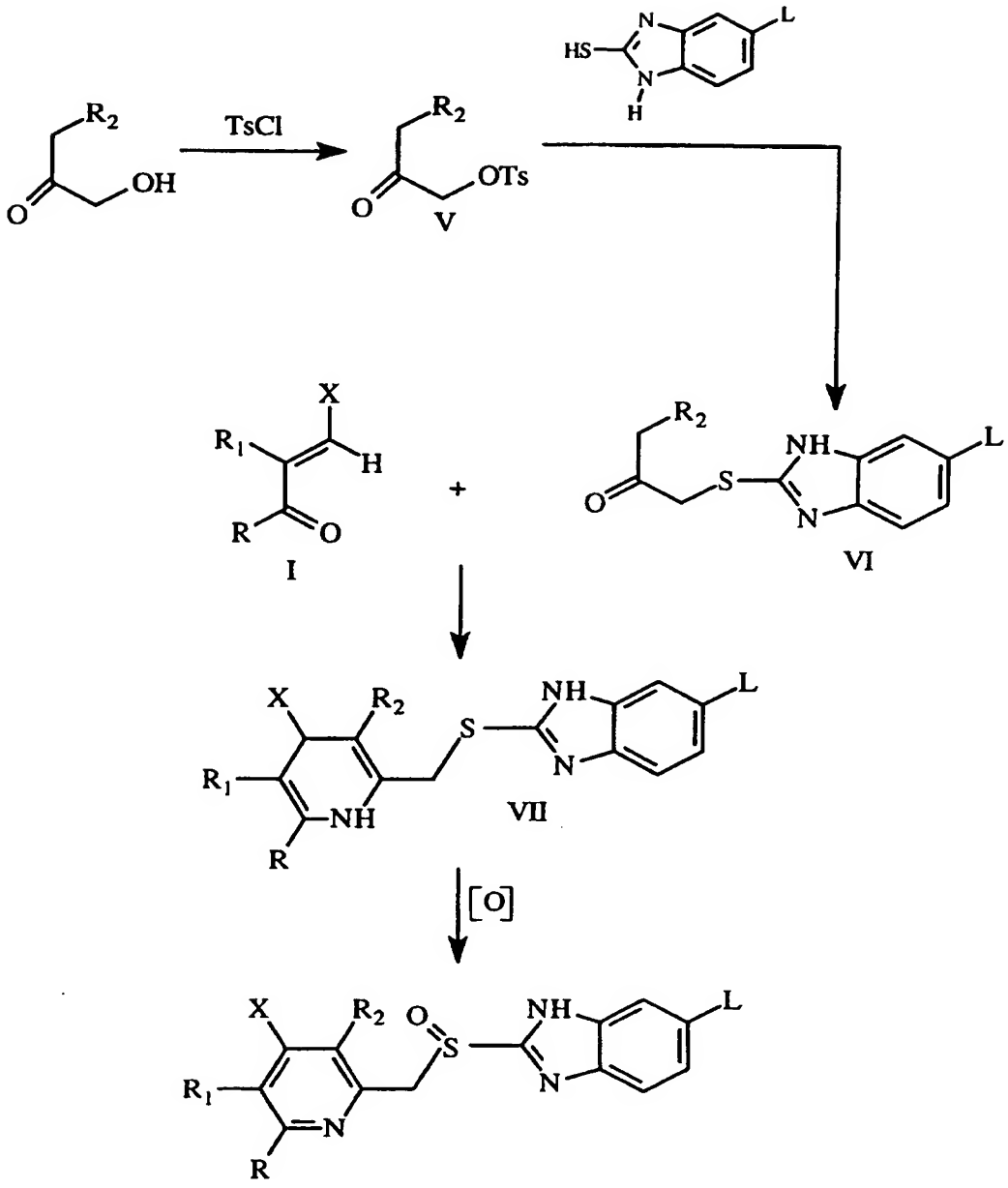
R_3 may be selected from the group consisting of:

Alkoxy
Hydroxy
Halogen
Activated Ester
Tosylate
Mesylate
Thiol
Xanthyl

and X may be selected from the group consisting of:

Alkoxy
Halogen
Nitro
Cyano
Carboxyl
Alkyl
H

11. The process of reacting:

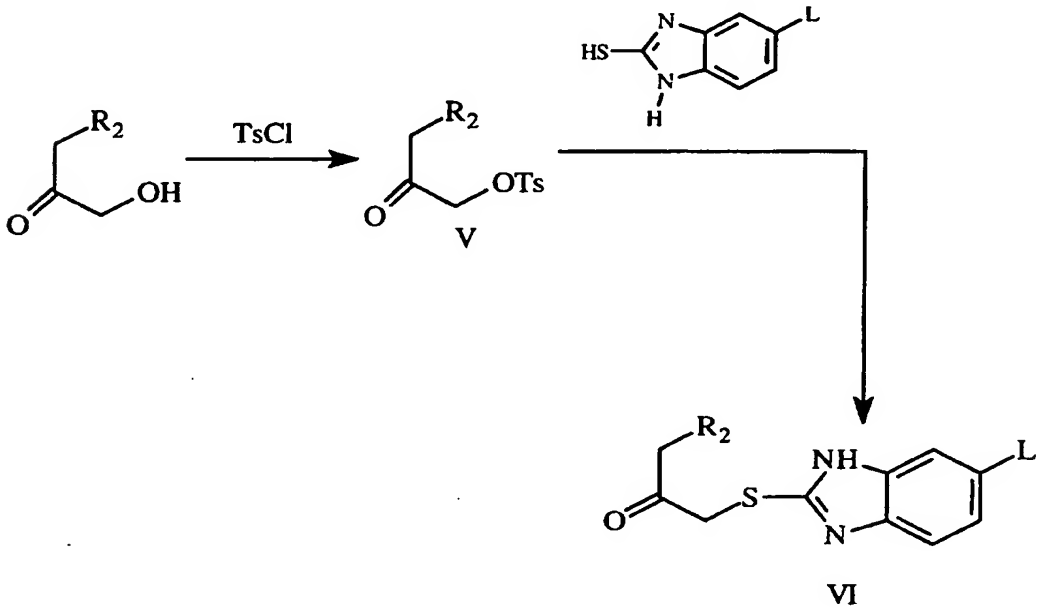


wherein R, R_1, R_2 and X are selected from:

R	R_1	R_2	X	To produce the Medicine identified below:
H	CH_3	CH_3	OCH_3	Omeprazole
H	H	OCH_3	OCH_3	Pantoprazole
H	H	CH_3	OCH_2CF_3	Lansoprazole

and L is selected from OCH_3 and OCH_2F.

12. The process of reacting:

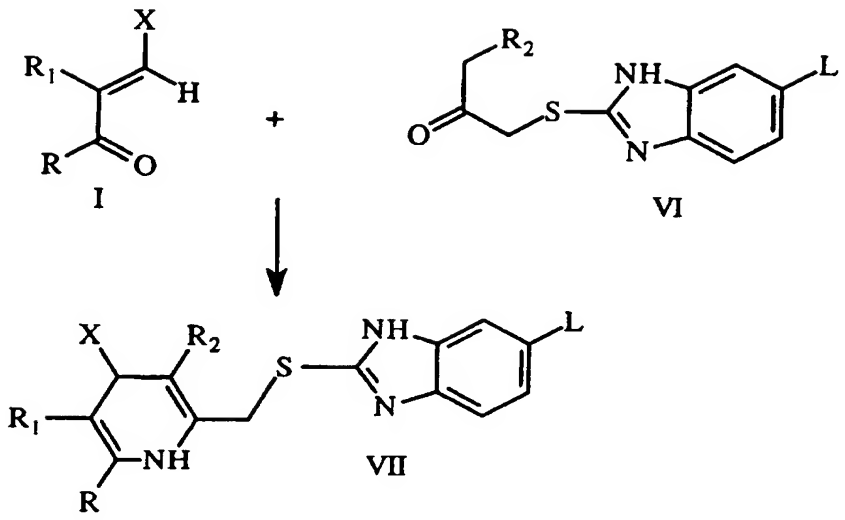


wherein R_2 is selected from:

R_2	To produce the Medicine identified below:
CH_3	Omeprazole
OCH_3	Pantoprazole
CH_3	Lansoprazole

and L is selected from OCH_3 and OCH_2F.

13. The process of reacting:

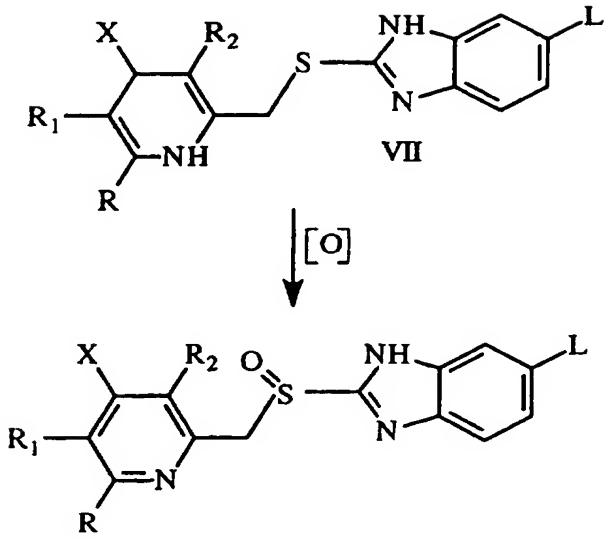


wherein R, R_1, R_2 and X are selected from:

R	R_1	R_2	X	To produce the Medicine identified below:
H	CH_3	CH_3	OCH_3	Omeprazole
H	H	OCH_3	OCH_3	Pantoprazole
H	H	CH_3	OCH_2CF_3	Lansoprazole

and L is selected from OCH_3 and OCH_2F.

14. The process of reacting:



wherein R, R_1, R_2 and X are selected from:

R	R_1	R_2	X	To produce the Medicine identified below:
H	CH_3	CH_3	OCH_3	Omeprazole
H	H	OCH_3	OCH_3	Pantoprazole
H	H	CH_3	OCH_2CF_3	Lansoprazole

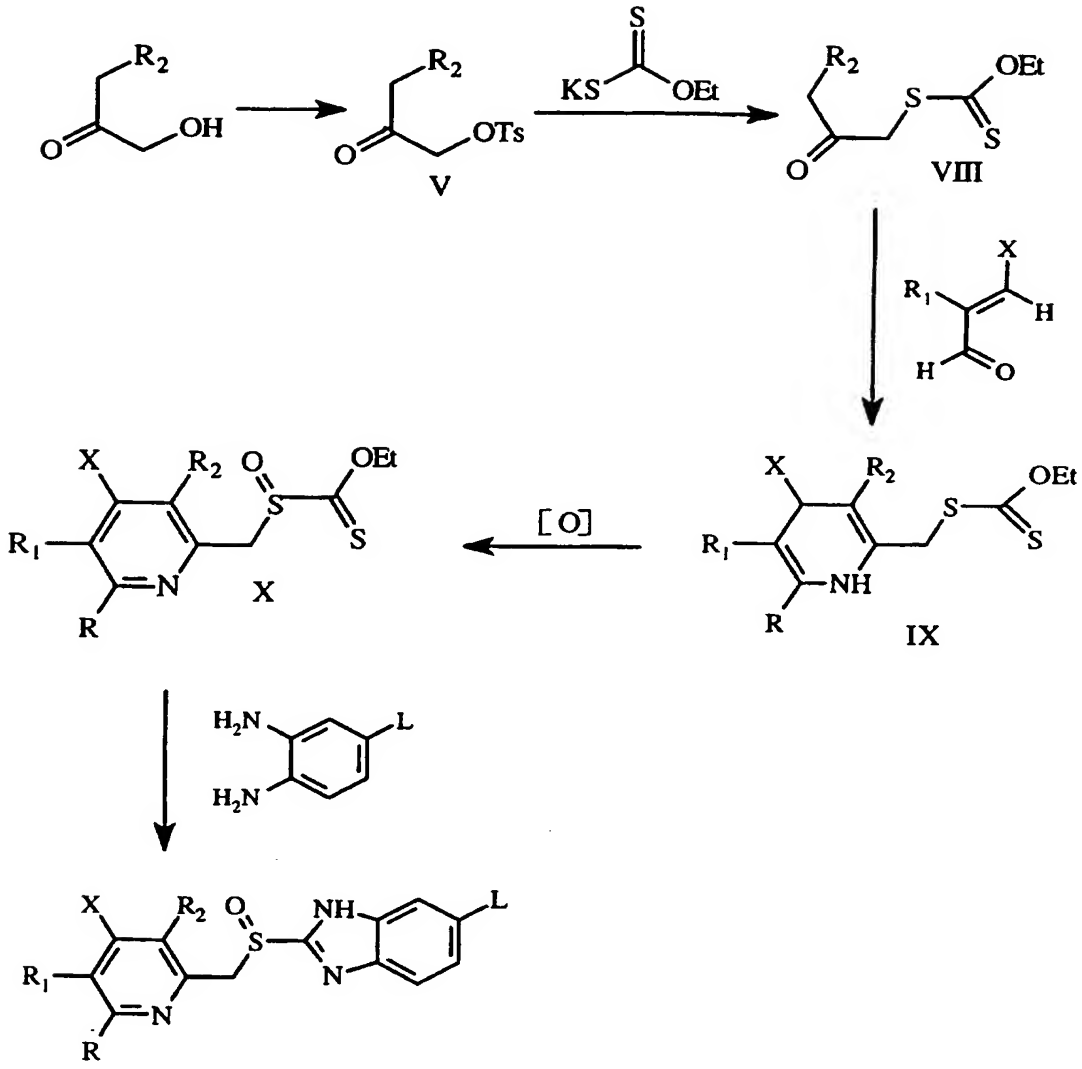
and L is selected from OCH_3 and OCH_2F.

15. The process of claim 14 wherein the medicine Omeprazole is produced.

16. The process of claim 14 wherein the medicine Pantoprazole is produced.

17. The process of claim 14 wherein the medicine Lansoprazole is produced.

18. The process of reacting:

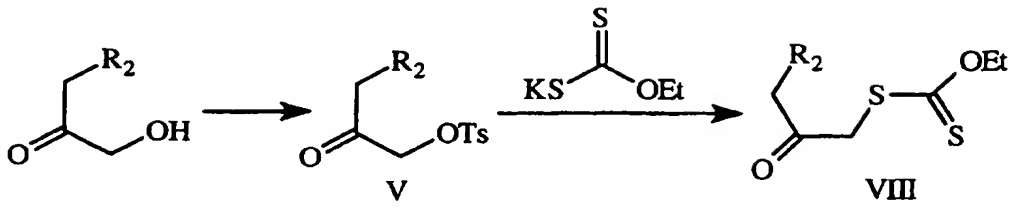


wherein R, R_1, R_2 and X are selected from:

R	R_1	R_2	X	To produce the Medicine identified below:
H	CH_3	CH_3	OCH_3	Omeprazole
H	H	OCH_3	OCH_3	Pantoprazole
H	H	CH_3	OCH_2CF_3	Lansoprazole

and L is selected from OCH_3 and OCH_2F.

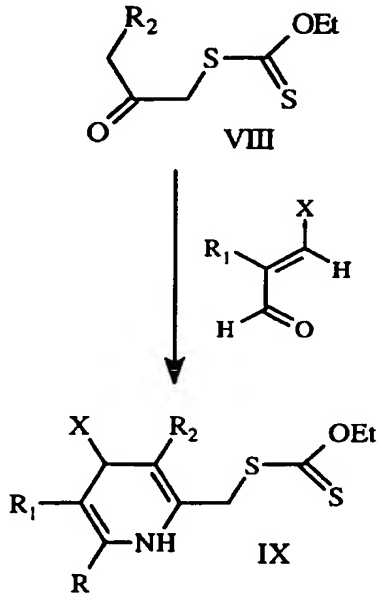
19. The process of reacting:



wherein R_2 is selected from:

R_2	To produce the Medicine identified below:
CH_3	Omeprazole
OCH_3	Pantoprazole
CH_3	Lansoprazole

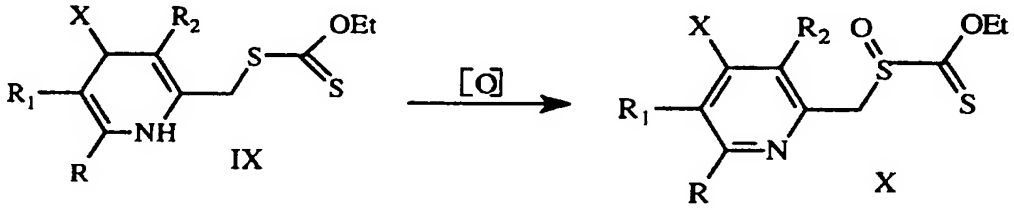
20. The process of reacting:



wherein R, R_1, R_2 and X are selected from:

R	R_1	R_2	X	To produce the Medicine identified below:
H	CH_3	CH_3	OCH_3	Omeprazole
H	H	OCH_3	OCH_3	Pantoprazole
H	H	CH_3	OCH_2CF_3	Lansoprazole

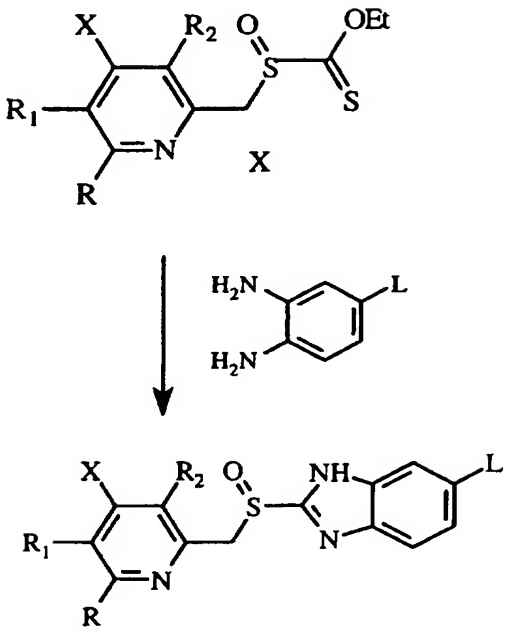
21. The process of reacting:



wherein R, R_1, R_2 and X are selected from:

R	R_1	R_2	X	To produce the Medicine identified below:
H	CH_3	CH_3	OCH_3	Omeprazole
H	H	OCH_3	OCH_3	Pantoprazole
H	H	CH_3	OCH_2CF_3	Lansoprazole

22. The process of reacting:



wherein R, R_1, R_2 and X are selected from:

R	R_1	R_2	X	To produce the Medicine identified below:
H	CH_3	CH_3	OCH_3	Omeprazole
H	H	OCH_3	OCH_3	Pantoprazole
H	H	CH_3	OCH_2CF_3	Lansoprazole

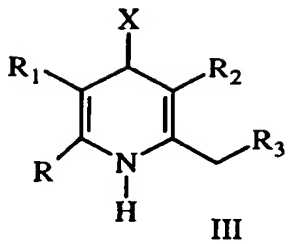
and L is selected from OCH_3 and OCH_2F.

23. The process of claim 18 or 22 wherein the medicine Omeprazole is produced.

24. The process of claim 18 or 22 wherein the medicine Pantoprazole is produced.

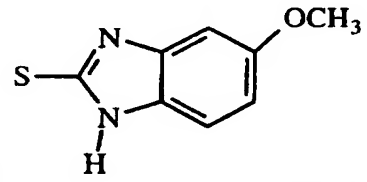
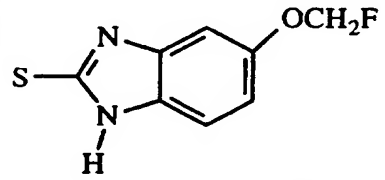
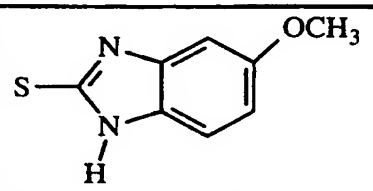
25. The process of claim 18 or 22 wherein the medicine Lansoprazole is produced.

26. The product:



III

wherein R, R_1, R_2, R_3 and X are selected from:

R	R_1	R_2	R_3	X	To produce the Medicine identified below:
H	CH_3	CH_3		OCH_3	Omeprazole
H	H	OCH_3		OCH_3	Pantoprazole
H	H	CH_3		OCH_2CF_3	Lansoprazole

or R may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

R_1 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_2 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

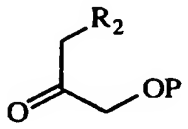
R_3 may be selected from the group consisting of:

Alkoxy
Hydroxy
Halogen
Activated Ester
Tosylate
Mesylate
Thiol
Xanthyl

and X may be selected from the group consisting of:

Alkoxy
Halogen
Nitro
Cyano
Carboxyl
Alkyl
H

27. The product:



P=Protecting Group

IIA

wherein R_2 is selected from:

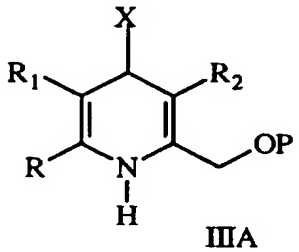
R_2	To produce the Medicine identified below:
CH_3	Omeprazole
OCH_3	Pantoprazole
CH_3	Lansoprazole

R_2 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

and P is a protecting group.

28. The product:



IIIA

wherein R, R_1, R_2 and X are selected from:

R	R_1	R_2	X	To produce the Medicine identified below:
H	CH_3	CH_3	OCH_3	Omeprazole
H	H	OCH_3	OCH_3	Pantoprazole
H	H	CH_3	OCH_2CF_3	Lansoprazole

or R may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_1 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_2 may be selected from the group consisting of:

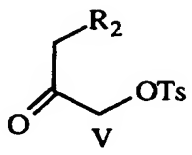
H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

and X may be selected from the group consisting of:

Alkoxy
Halogen
Nitro
Cyano
Carboxyl
Alkyl
H

and P is a protecting group.

29. The product:



wherein Ts is Tosylate and R_2 is selected from:

R_2	To produce the Medicine identified below:
CH_3	Omeprazole
OCH_3	Pantoprazole
CH_3	Lansoprazole

or R_2 may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

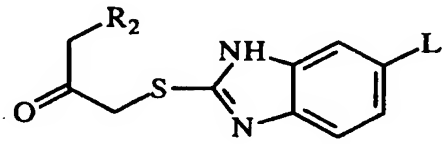
Esters

Cyano

Thiol

Xanthyl

30. The product:



VI

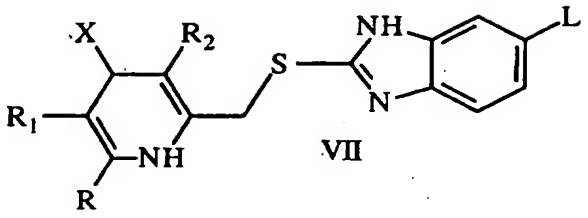
wherein R_2 and L are selected from:

R_2	To produce the Medicine identified below:
CH_3	Omeprazole
OCH_3	Pantoprazole
CH_3	Lansoprazole

or R_2 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

31. The product:



VII

wherein R, R_1, R_2, X and L are selected from:

R	R_1	R_2	X	To produce the Medicine identified below:
H	CH_3	CH_3	OCH_3	Omeprazole
H	H	OCH_3	OCH_3	Pantoprazole
H	H	CH_3	OCH_2CF_3	Lansoprazole

or R may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_1 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

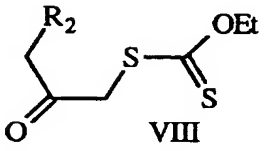
R_2 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

and X may be selected from the group consisting of:

Alkoxy
Halogen
Nitro
Cyano
Carboxyl
Alkyl
H

32. The product:



VIII

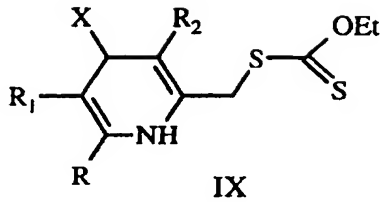
wherein R2 is selected from:

R_2	To produce the Medicine identified below:
CH_3	Omeprazole
OCH_3	Pantoprazole
CH_3	Lansoprazole

or R_2 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

33. The product:



IX

wherein R, R_1, R_2 and X are selected from:

R	R_1	R_2	X	To produce the Medicine identified below:
H	CH_3	CH_3	OCH_3	Omeprazole
H	H	OCH_3	OCH_3	Pantoprazole
H	H	CH_3	OCH_2CF_3	Lansoprazole

or R may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_1 may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_2 may be selected from the group consisting of:

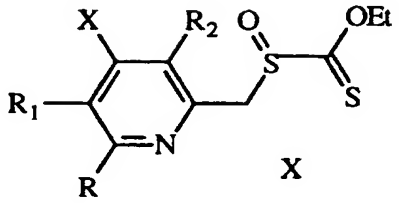
H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

and X may be selected from the group consisting of:

Alkoxy
Halogen
Nitro
Cyano
Carboxyl
Alkyl
H

and Et is ethyl.

34. The product:



wherein R, R_1, R_2 and X are selected from:

R	R_1	R_2	X	To produce the Medicine identified below:
H	CH_3	CH_3	OCH_3	Omeprazole
H	H	OCH_3	OCH_3	Pantoprazole
H	H	CH_3	OCH_2CF_3	Lansoprazole

or R may be selected from the group consisting of:

H
Alkyl (1-3C)
Carboxyl acid
Esters
Cyano

R_1 may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

R_2 may be selected from the group consisting of:

H

Alkyl (1-3C)

Carboxyl acid

Esters

Cyano

and X may be selected from the group consisting of:

Alkoxy

Halogen

Nitro

Cyano

Carboxyl

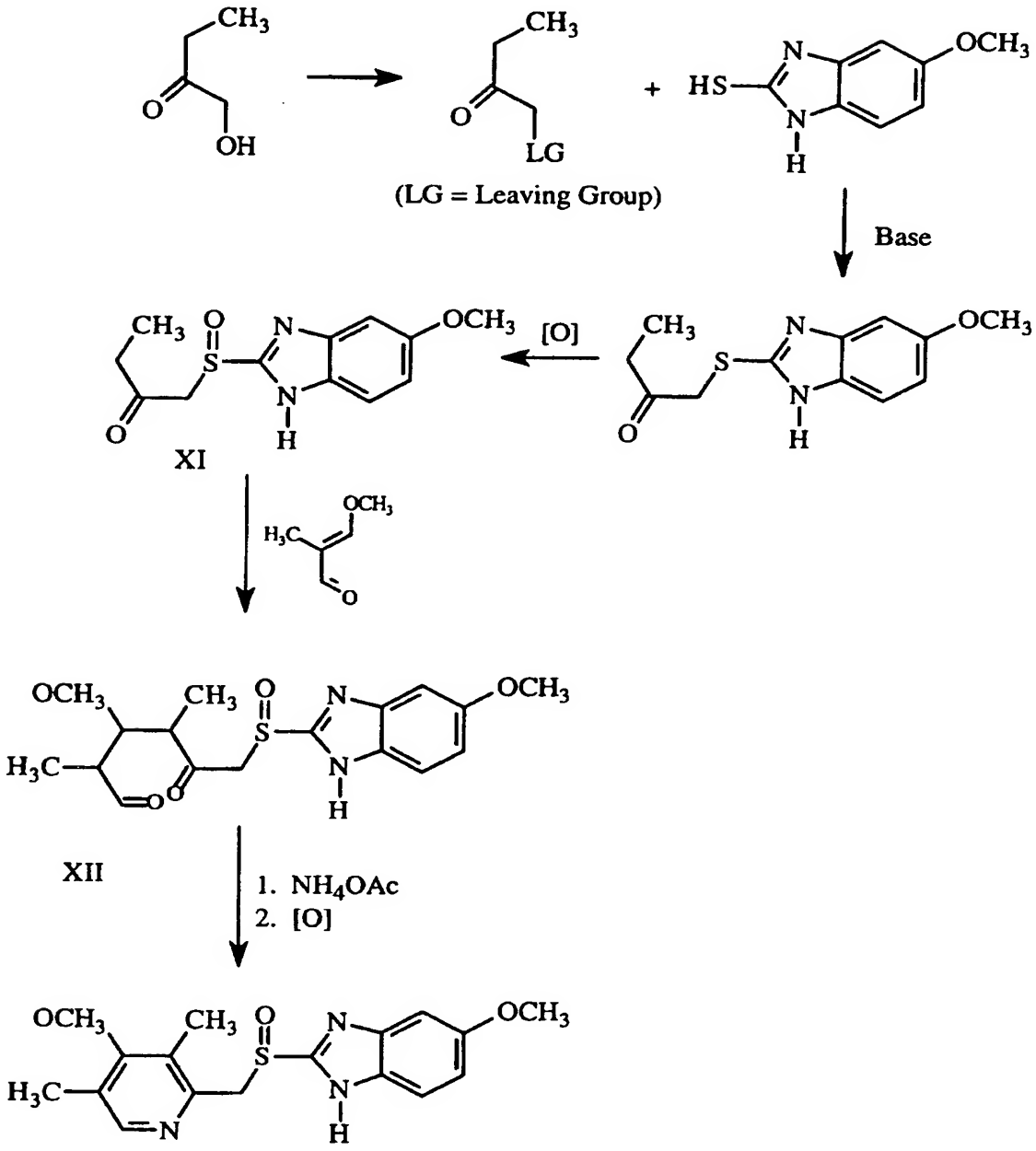
Alkyl

H

and Et is ethyl.

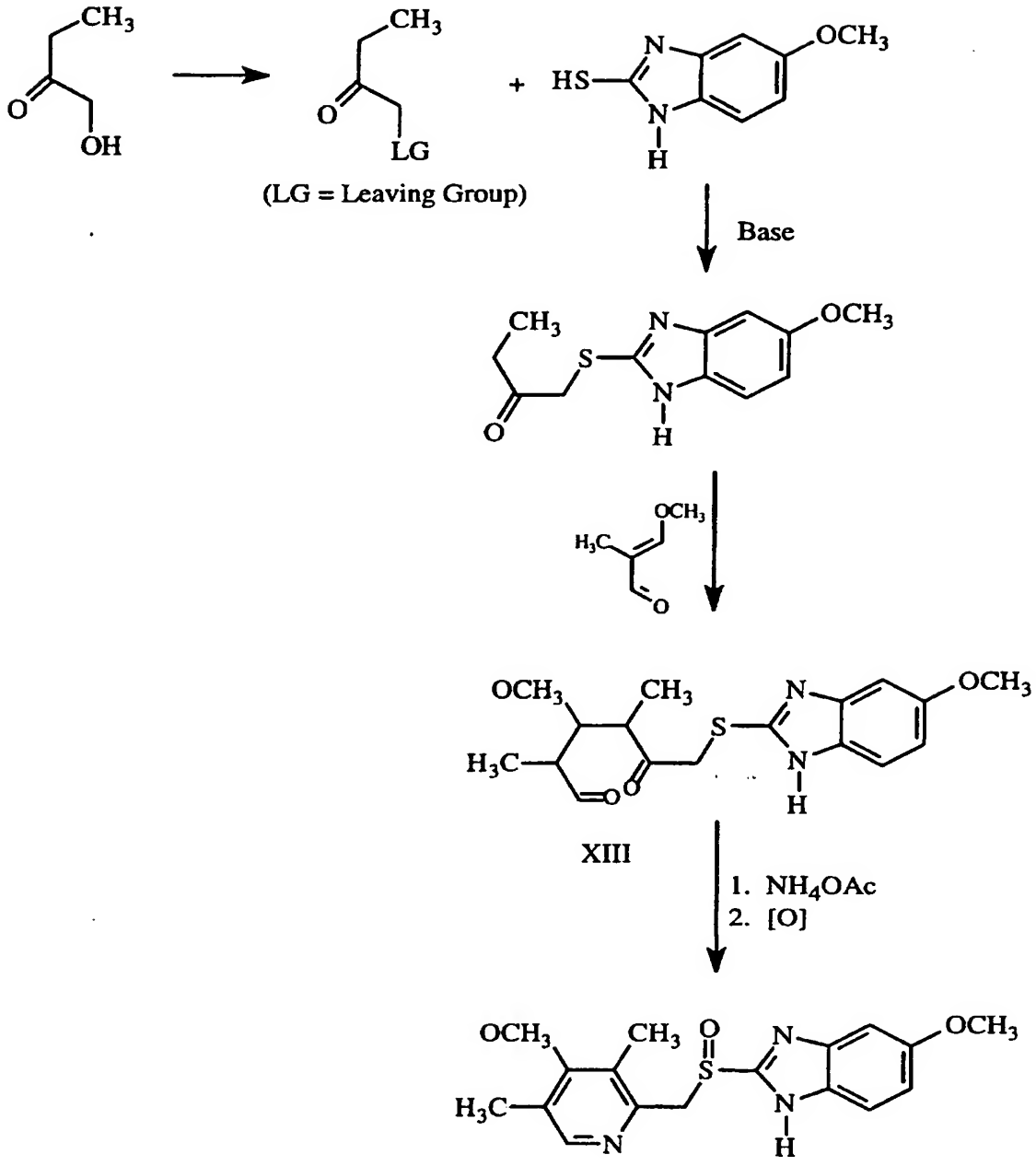
35. The process:

Route I

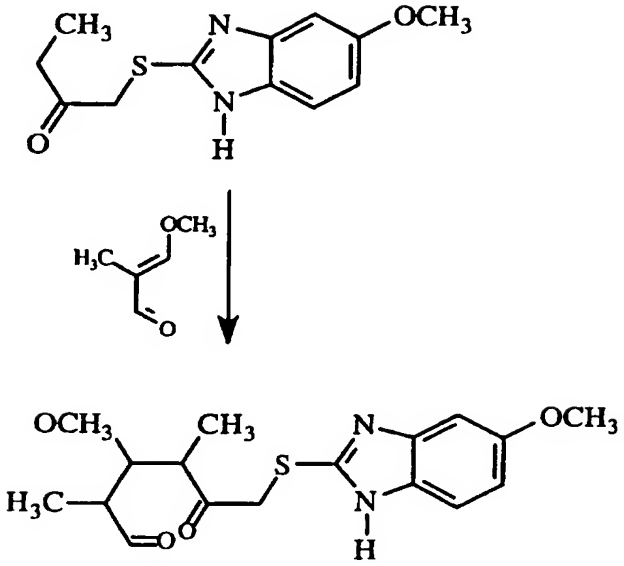


36. The process:

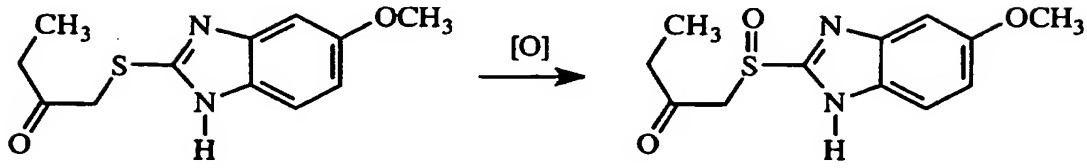
Route II



37. The process:



38. The process:



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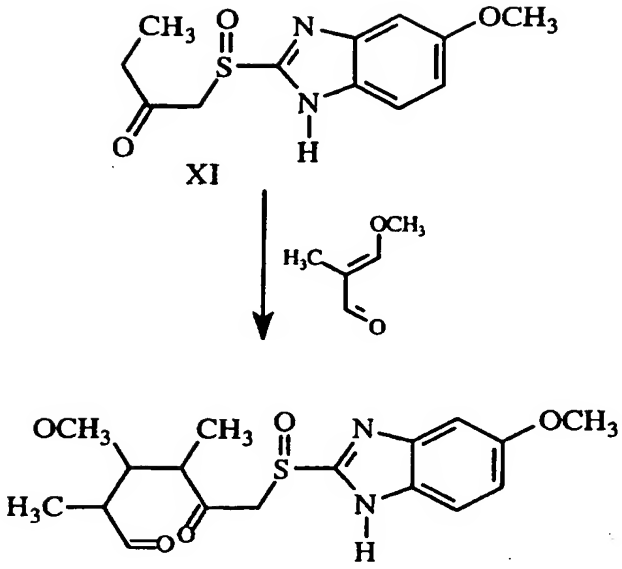
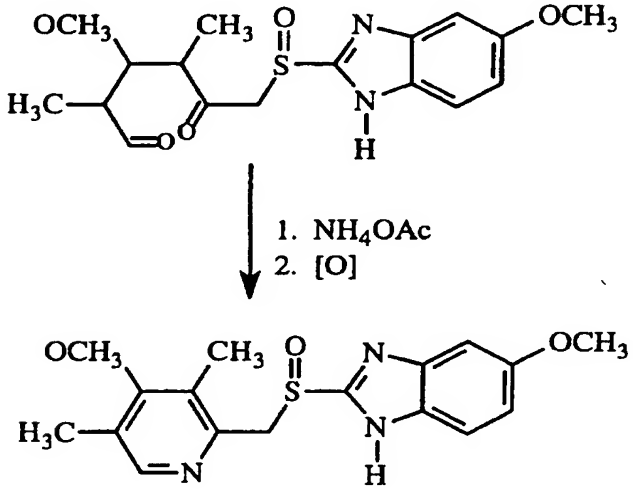


XI

40. The process:



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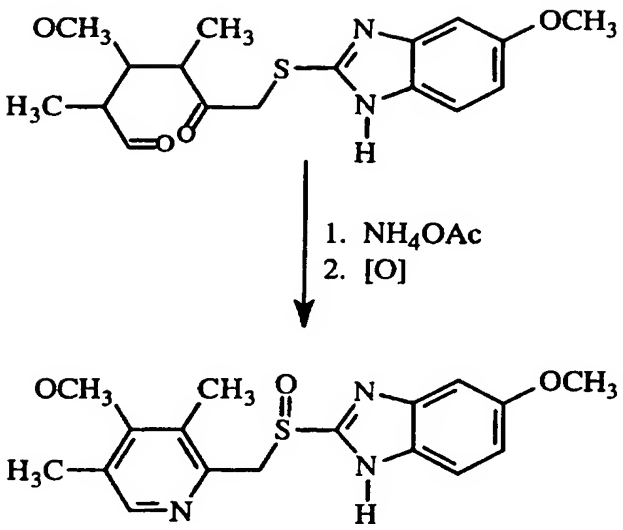

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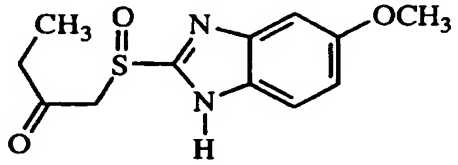

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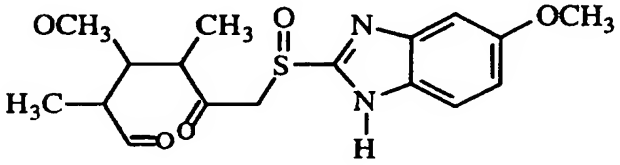

44. The product: